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Uraemic symptom burden and clinical condition in women and men of 65 years of age and older with advanced CKD: results from the EQUAL study.

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Abstract

Background: The epidemiology and prognosis of chronic kidney disease (CKD) differ by sex. We aimed to compare symptom prevalence and the clinical state in women and men of 65 years of age and over with advanced CKD receiving routine nephrology care.

Methods: The EQUAL Study follows patients from 6 European countries of 65+ years whose eGFR dropped to ≤20 ml/min/1.73m^2 for the first time during the last six months.

The Dialysis Symptom Index was used to assess the prevalence and severity of uraemic symptoms. Data on the clinical state at baseline were collected from medical records. Prevalence was standardised using the age distribution of women as the reference.

Results: Women (n=512) and men (n=967) did not differ regarding age (77.0 vs 75.7 years) and eGFR (19.0 vs 18.5).The median number of symptoms 14/33 (IQR 9-19) in women, and 11/33 (IQR 7-16) in men. Women most frequently reported fatigue (39% [95%CI 34-45]) and bone/joint pain (37% [95%CI 32-42]) as severe symptoms, whereas more men reported difficulty in becoming sexually aroused (32% [95%CI 28-35]) and a decreased interest in sex (31% [95%CI 28-35]). Anaemia (73% [95%CI 69-77] vs 85% [95%CI 82-87]) was less common in women than in men, just as smoking history and cardiovascular comorbidity. However, a diagnosis of liver disease other than cirrhosis, psychiatric disease, and mild malnutrition were more common among women.

Conclusions: Women in secondary care with an incident eGFR =< 20 ml/min/1.73m2 reported a higher symptom burden, while their clinical state was considered similar or even more favourable as compared to men.

Introduction

There are several differences between women and men concerning the epidemiology and prognosis of chronic kidney disease (CKD).(1-3) The population in the early stages of CKD comprises more women, whereas men start to outnumber women in CKD stages 4 and 5.(4-7) Kidney function decline is faster in men (8-10) and (all-cause) mortality has been suggested to differ by sex as well, although results are inconclusive.(8, 11-14)

Less is known about sex differences in as the manifestation of disease. While symptom burden for patients with advanced CKD has been suggested to be similar to that in end-stage kidney disease (ESKD), multidimensional symptom burden in CKD is still a relatively understudied topic.(15) In the few studies that focused on patients being managed conservatively without dialysis,(16-18) the average number of symptoms ranged from 7 to 12 (17, 18) symptoms per patient, and more than half of the patients reported the presence of fatigue, pruritus, drowsiness, dyspnea, swelling of the legs, pain, dry mouth, and muscle cramps.(17) Also, de Goeij et al. showed that the number of symptoms, especially fatigue and loss of strength, increased during pre-dialysis care.(19) Data on sex differences in the clinical condition in patients not on dialysis are limited. One study from the UK showed that hypertension and obesity were more common in women with a kidney function <30 ml/min/1.73m^2, whereas diabetes was less common.(20)

The symptom patterns and burden are known to increase with age, so it is essential to stratify by age groups.(21) If there are differences in the manifestation of advanced CKD between women and men, this could influence decision-making processes and further improve personalised care. We therefore aimed to assess whether the presence of uraemic symptoms and the patient's clinical condition differ by sex in patients of 65 years of age and over with advanced CKD.

Methods

Study design and study population

The EQUAL study is a prospective cohort study in advanced CKD patients in Germany, Italy, Poland, Sweden, The Netherlands and the United Kingdom. Approval was obtained from the medical ethical committees of the national coordinating centers, and corresponding institutional review boards of the participating centers. Written informed consent was obtained from all patients. A full description of the study has been published elsewhere.(22)

Patients of 65 years and older were included if their eGFR, as estimated by the MDRD equation, had dropped for the first time to 20 ml/min/1.73m^2 or lower during the previous six months. Patients were eligible when they were followed in a nephrology clinic, but were excluded if the drop in eGFR resulted from an acute event, or if the patient had received any form of RRT in the past. We used the baseline data of all patients who were recruited for the EQUAL study between March 2012 and December 2015.

Data collection

Data on the clinical condition of patients were obtained from medical records and entered in a web-based clinical record form (eCRF). The eCRF included information on the patients' demographics, ethnicity, kidney disease, comorbid conditions, diet,medication, physical examination, and local routine laboratory results. In order to standardize laboratory results, all participating centres completed a questionnaire to capture details on local laboratory methods, units of measurement and normal ranges. Physical examination at the local participating sites was performed through standard protocols.

Data regarding the patient's lifestyle, marital status, and the presence and burden of 33 uraemic symptoms related to advanced CKD was obtained through self-administered paper patient questionnaires translated to the native language of the country of the patient. The list

of symptoms was based on the validated Dialysis Symptom Index (23) and complemented with the items bleeding, loss of weight, and loss of strength. Patients had to score the presence of these symptoms over the past month. For each symptom present, patients rated symptom severity using a 5-point scale with the options “not at all”, “a little bit”, ”somewhat”, ”quite a bit”, or “very much”.

The clinical state of the patient included signs of uraemia (urea, anemia, and parathyroid hormone [PTH]), comorbid conditions according to the Charlson comorbidity index,(24) and nutritional status expressed as level of protein energy wasting following the subjective global assessment (SGA). Furthermore, we included the cardiovascular risk profile which was based on smoking status, body mass index (BMI), blood pressure, cholesterol, diabetes mellitus, and a history of the following cardiovascular comorbid conditions: cerebrovascular disease, peripheral vascular disease, coronary artery disease, myocardial infarction, angina pectoris, congestive heart failure, left ventricular hypertrophy, and atrial fibrillation.

Statistical analysis

Patient characteristics are reported as mean values with standard deviations (sd) for normally distributed data, median values with interquartile ranges (IQR) for not normally distributed data, and as proportions for categorical variables. With the chi-square, student’s t-test, or their non-parametric equivalents we tested for differences by sex.

We calculated the prevalence and 95% confidence intervals (CI) of severe uraemic symptoms for all patients and women and men separately. Symptoms were considered severe when rated as ”quite a bit”, or “very much”.

To adjust for potential effects of patient age on symptoms and clinical condition, we standardised the prevalence using the age distribution of women as the reference. The age

standardised prevalence was tested for statistically significant differences between women and men using Chi-square tests.

The total number of *all* uraemic symptoms (i.e. irrespective of severity), as well as for severe symptoms only were calculated. Using linear regression analysis, we subsequently tested the association between the sum of uraemic symptoms and eGFR in women and men separately.

We calculated the prevalence of uraemic signs as a composite measure of the percentage of patients above (or below) a certain threshold combined, where appropriate with any relevant drug prescriptions. Cut-off levels and groups of relevant drugs were determined based on the existing literature describing reference values for uraemic signs in the CKD population and on expert opinion from the EQUAL collaborators. We applied the following thresholds; urea ≥25mmol/L, Hb <7.5 mmol/L for women and Hb <8.1 mmol/L for men (which translates to Hb levels below 120 and 130 g/L, respectively),(25) PTH ≥ 65 pmol/L(26). Relevant drug groups based on ATC codes were H05B (preparations inhibiting uric acid production), M04AA (anti-parathyroid agents), and B03 (anti-anaemic preparations). Furthermore, we calculated the age standardised prevalence of cardiovascular risk factors and disease, nutritional status, and any additional comorbidities, using the following cutoff levels: diastolic blood pressure >85 mmHg, systolic blood pressure >140 mmHg, and a total cholesterol level >5.2 mmol/L or the prescription of lipid modifying agents (ATC codes in group C10). All analyses were performed using SAS v9.4, and p-values below 0.05 were considered statistically significant.

Results

The demographic and clinical characteristics of the study population are described in Table 1. Clinical data were available for 1,479 patients, of which 1,077 returned the completed questionnaire. The median age was 76.1 years (IQR 70.7 to 81.3), and 35% of the population were women. The most frequent causes of kidney disease were hypertension (35%) and diabetes mellitus (20%). Age did not significantly differ between women and men (women: 77.0 [IQR 71.1 to 82.3] vs men: 75.7 [IQR 70.6 to 80.8] years, p=0.05), and women were less often married or living together (45% vs 74%). Median baseline eGFR was 18.7 (IQR 15.3 to 22.1) ml/min/1.73m^2, but did not differ by sex, whereas time since CKD diagnosis was shorter in women. Levels of creatinine, urea, and Hb were lower in women than in men, whereas cholesterol levels were higher.

Uraemic symptoms

Figure 1 shows the presence of uraemic symptoms in women and men and indicates the proportion of patients who perceived the symptoms as severe. The most frequently reported symptoms by women were fatigue (78.1%), bone or joint pain (70.9%), and dry skin (69.1%). In men, these were fatigue (66.8%), difficulty in becoming sexually aroused (61.5%), and decreased interest in sex (58.5%). More than 50% of both women and men reported the symptoms fatigue, dry skin, bone or joint pain, loss of strength, muscle cramps, itching, and a decreased interest in sex. Virtually all symptoms were more often reported by women. Statistically significant differences are indicated in Figure 1.

Figure 2 shows the age standardised prevalence of severe symptoms among women and men. Although some differences did not differ statistically significantly, all symptoms tended to be more prevalent in women except bleeding, decreased interest in sex, and difficulty in becoming sexually aroused. Moreover, the prevalence of nausea, vomiting,

decreased appetite, muscle cramps, leg swelling, restless legs, dry mouth, bone or joint pain, headache, muscle soreness, dry skin, worrying, feeling nervous, and feeling anxious was at least twice as high in women as in men.

The median number of severe uraemic symptoms was 2 (IQR 1 to 5) for both sexes, 4 (IQR 1 to 7) in women, and 2 (IQR 0 to 4) in men. Irrespective of severity, the median number of symptoms for all patients was 12 (IQR 8 to 17), 14 (IQR 9 to 19) in women, and 11 (IQR 7 to 16) in men. There was no association between eGFR and the number of symptoms in both sexes (women, p=0.78, men, p=0.60).

Clinical condition

The clinical status of the patient is described in Figure 3. Anemia was less prevalent among women (73.0% [95%CI 69.1% to 76.9%]) compared to men (84.7% [95%CI 82.0% to 87.0%]. On the other hand, high levels of urea were observed in 17.5% (95% CI 14.1% to 20.8%) of women opposed to 22.0% (95% CI 19.5% to 24.7%) in men. The age adjusted prevalence of cardiovascular risk factors showed that women tended to be less often overweight compared to men (31.4%, 95%CI 26.0 to 36.9% vs 39.9%, 95%CI 36.3% to 44.0%, respectively), but tended to be more often obese (36.7%, 95%CI 31.1% to 42.4% vs 31.2%, 95% CI 27.9% to 35.0%). The sex difference disappeared when combining these two categories into a BMI of 25 kg/m2 and higher. Women had smoked significantly less often, and a diagnosis of peripheral vascular disease, angina pectoris, coronary artery disease, and myocardial infarction and malignancy was less common among women. However, diagnoses of liver disease other than cirrhosis, psychiatric disease, and mild malnutrition were more frequent among women.

Discussion

In patients of 65 years of age and over with advanced CKD, the clinical manifestation of CKD regarding uraemic symptoms and clinical condition differs between women and men. We show that virtually all self-reported uraemic symptoms related to advanced CKD were more common in women compared with men, whereas anemia, high urea and cardiovascular risk factors were less prevalent amongst women. In contrast, women had a higher prevalence of liver disease other than cirrhosis, psychiatric disease, and mild malnutrition.

The overall symptom burden in this advanced CKD population was substantial. More than half of all patients reported the presence of fatigue, dry skin, bone or joint pain, loss of strength, muscle cramps, dry mouth, itching, and a decreased interest in sex, with a median of 12 out of 33 symptoms per patient. This is in line with data from Murtagh et al. and Yong et al. who found a mean of 11.6 out of 28 (SD 5.2) symptoms using the Memorial Symptom Assessment Scale Short Form and 8.3 out of 23 (SD 3.9) symptoms per patient using a list of symptoms based on literature review and expert opinion, respectively (17, 18, 27, 28). Importantly, we demonstrate that symptoms were more prevalent in women (14/33) compared with men (11/33) in general, which was also the case when focusing specifically on symptoms that were perceived as severe. Our data also showed differences in the type of uraemic symptoms between women and men. Symptoms such as bone or joint pain, leg swelling, trouble staying asleep, shortness of breath were predominantly reported by women, while men more often reported difficulty in becoming sexually aroused and a decreased interest in sex In this respect, advanced CKD follows other chronic disease populations, where women also report a lower health related quality of life compared with men.(29) Although the self-reported presence of uraemic symptoms may reflect a “subjective” measure of the severity of disease, the different prevalence of patient-reported symptom burden observed in men and

women implies that disease manifestation, or at least disease perception, is worse in women than in men.

In the general population, women are also more likely to report symptoms than men.(30-32) Among the general population of 65 to 79 years of age in Sweden,(33) pain in limbs was the most frequently reported symptom by both women (43.3%) and men (31.1%). In the same population, tiredness/weakness was prevalent amongst 29% of women and 22% of men. In our study population, the prevalence of fatigue was substantially higher (80.0% in women, 70.8% in men). Similar results were found when comparing sleeplessness in the general Swedish population (27% in women, 15% in men) with 'trouble staying asleep' among the advanced CKD population (56.4% in women, 45.7% in men), and when comparing melancholy (16% in women, 8% in men) versus 'feeling sad' (47.0% in women, 31.9% in men). This suggests that symptom burden among advanced CKD patients of 65 years of age and over may be double or even triple compared to that of the general population of 65 to 79 years of age.

Several mechanisms have been described that could contribute to sex differences in symptom burden in general. Some diseases such as depression and anxiety disorders with accompanying somatic symptoms are more common in women.(15) Also, the perception of pain and bodily awareness and vigilance might be increased due to biological differences. Finally, women have a lower threshold to consult a clinician and seek medical care. (30) Specifically for this population, the higher symptom burden for women at an eGFR level of 20 ml/min/1.73m2, suggests that there might be less scope for symptom burden to increase during the course of disease compared to men. This could mean that the symptom burden should be incorporated differently in the decision-making process about dialysis initiation for women and men, suggesting that other factors in the decision-making are important for men

and women. However, this speculation requires further studies incorporating longitudinal data to evaluate the changes over time and changes due to disease progression.

In contrast to the self-reported presence of uraemic symptoms, the patients' clinical condition may represent a more "objective" measure, as this will have been assessed and diagnosed by clinicians. Assessment of the clinical condition showed that lower Hb levels were more common in men. This is consistent with the literature on sex differences in anaemia in the patients of advanced age.(34-38) The more favourable cardiovascular risk profile in women is in line with the findings of Carrero et al. in incident patients on dialysis(35), and has been attributed to the decades long protective effect of estrogens in women.(38) Despite cardiovascular disease being the leading cause of death in both European men and women, it is still considered a men's disease.(39, 40) In advanced CKD, our data show that this is the case for peripheral vascular disease, coronary artery disease, myocardial infarction, and angina, where for the latter three the prevalence among men was twice as high as in women. The lower prevalence of coronary artery disease in women may reflect the lower prevalence of present and previous smoking in women, but may also be attributed to a different presentation, symptom pattern, or lower physician awareness for coronary artery disease in women, and thus under-recognition of this disease among women.(41)

In line with the general population, psychiatric disease, and liver disease other than cirrhosis were observed more frequently among women.(42) Furthermore, despite similar serum albumin, significantly more women than men had a moderate level of protein energy wasting based on the 7 points SGA method. This confirms the results from Westland et al., who showed that age, female sex, and BMI were independently associated with moderate levels of protein energy wasting among pre-dialysis patients. A study by Windahl et al. focused in more detail on the prevalence of protein energy wasting among EQUAL Study participants. Their data showed that the risk of protein energy wasting substantially increases

with age, and that muscle wasting was the main contributor.(submitted). The tremendous consequences of protein energy wasting on hospitalisation rates, impaired quality of life, and mortality stress that strict monitoring and managing of nutritional status is important, and should start early on in the course of CKD. The discrepancy between the prevalence of protein energy wasting and low serum albumin is in agreement with previous studies showing that serum albumin is a poor nutritional marker in patients with CKD, and that serum albumin is mainly related to other factors such as chronic inflammation and renal albumin losses.(43, 44)

The main strength of this study is that we were able to examine a unique cohort of patients of 65 years of age and over with advanced CKD with extensive clinical data, stratified by sex. In line with the advanced CKD and dialysis population, our cohort predominantly consists of men. Limitations include the possibility that symptoms were over reported, as it is easier to recall their presence from a pre-defined list. There is, however, no reason to suspect this recall bias would be different in women and men, or different in advanced CKD compared with other chronic diseases or the general population. Secondly, although the dialysis symptom index is the most commonly used extensive symptom list(45), it does not register the frequency and duration of symptoms, and therefore does not completely capture the total symptom burden. Finally, the EQUAL study follows patients during routine clinical practice, meaning that recruitment was predominantly based on eGFR MDRD equations. However, the classification of patients into different stages of CKD varies according to the equation used. Women are more likely to be misclassified as having CKD when using the MDRD equation compared to the CKD-epi equation, as MDRD estimates lower levels of GFR.(46-48) This potential misclassification is in line with the more

favourable clinical condition in women but in sharp contrast with their increased uraemic symptom burden.

In conclusion, we found that symptom burden is high in patients of 65 years of age and over with advanced CKD and the clinical manifestation of the disease differs substantially between women and men, which is in line with findings in other chronic diseases and the general population. Whereas symptom burden was higher in women, the clinical condition in terms of uraemic signs and cardiovascular risk factors and disease was usually similar or even favourable compared to men.

The high symptom burden in general and the even greater burden in women versus men warrant further research given the detrimental effects of symptoms on a patient's quality of life.(27, 28) We suggest performing further studies with separate analyses for women and men, for example regarding changes in health status during the course of CKD and when exploring opportunities for the alleviation of symptoms. This could help tailor personalised treatment strategies and decision-making on if and when to start dialysis.

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Conflict of interest

The authors have had no involvements that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated. None of the sponsors were involved in study design, collection of data, statistical analyses, interpretation of data, writing of the manuscript, or in the decision to submit the paper for publication. The results presented in this paper have not been published previously in whole or part.

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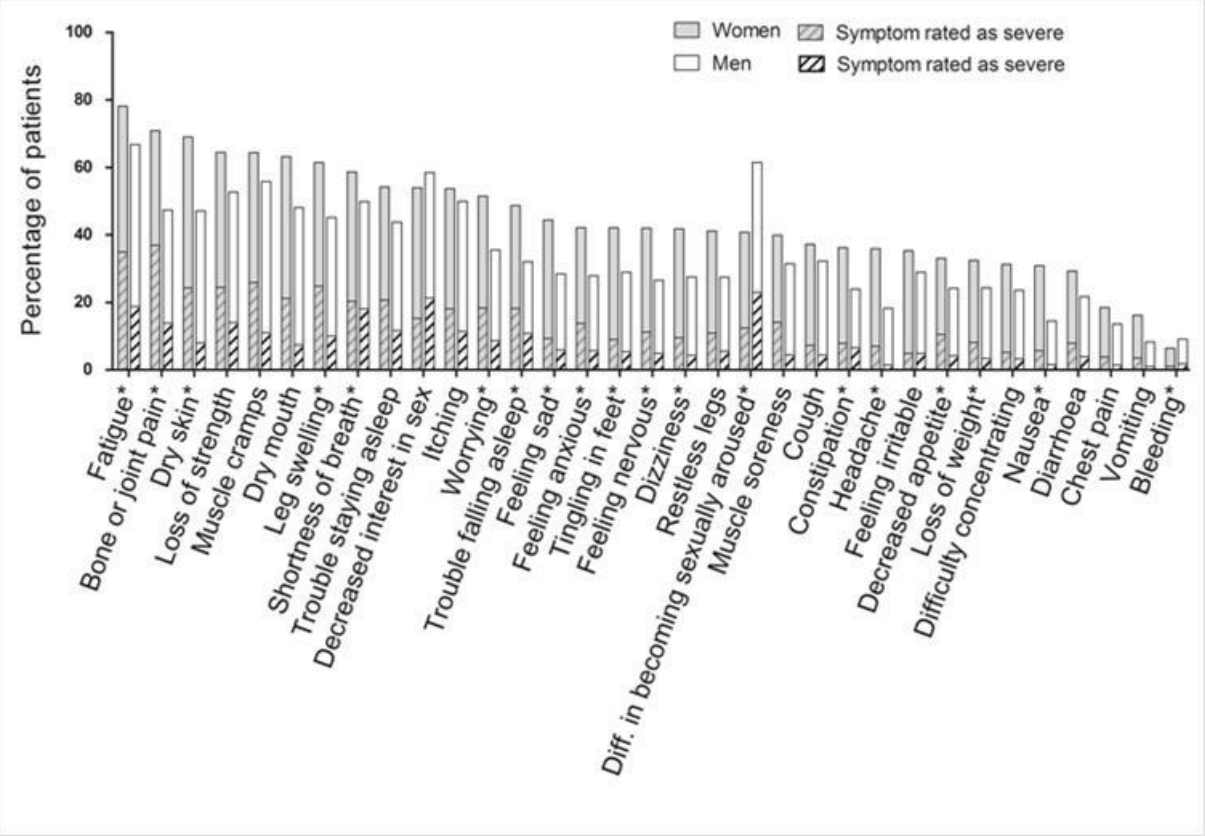
Table and Figures

Table 1: Demographic and clinical characteristics of the study cohort

		All n=1479	Women n=512 (35%)	Men n=967 (65%)	p-value
Age - Median (IQR)		76.1 (70.7-81.3)	77.0 (71.1-82.3)	75.7 (70.6-80.8)	0.05
Marital status[1]	Married/Living together	689 (64%)	165 (45%)	524 (74%)	<0.001
	Divorced/ separated	89 (8%)	37 (10%)	52 (7%)	
	Widowed/Partner has died	246 (23%)	144 (39%)	110 (14%)	
	Never married/lived with partner	53 (5%)	21 (6%)	32 (5%)	
eGFR - median (IQR)		18.7 (15.3-22.1)	19.0 (15.5-22.6)	18.5 (15.2-21.7)	0.29
PRD	Glomerular disease	125 (8%)	36 (7%)	89 (9%)	0.31
	Tubulo-interstitial disease	121 (8%)	54 (11%)	67 (7%)	
	Systemic disease affecting the kidney	35(2%)	13 (3%)	22 (2%)	
	Diabetes	299 (20%)	90 (18%)	209 (22%)	
	Hypertension	518 (35%)	188 (37%)	330 (34%)	
	Familial/Hereditary nephropathies	47 (3%)	18 (4%)	29 (3%)	
	Miscellaneous renal disorders	52 (4%)	10 (2%)	42 (4%)	
	Unknown/missing	282 (19%)	103 (20%)	179 (19%)	
Years since diagnosis	median (IQR)	3 (1-7)	2 (1-7)	3 (1-7)	<0.05
BMI (kg/m^2)	mean ± std	28.4 ± 5.4	28.8 ± 6.3	28.2 ± 4.9	0.07
Blood pressure	Systolic blood pressure (mmHg)	140 (130-157)	140 (128-155)	140 (130-157)	0.09
	Diastolic bp (mmHg)	73 (66-80)	72 (67-80)	73 (66-81)	0.33
Laboratory data	Creatinine (μmol/L)	276 (226-332)	226 (192-271)	299 (259-354)	<0.05
	Urea (mmol/L)	19.3 (15.5-24.0)	18.2 (14.1-23.2)	19.6 (16.2-24.3)	<0.05
	Albumin (g/L)	38.0 (35-41)	38 (34-41)	38 (35-41)	0.99
	Haemoglobin (mmol/L)	7.2 ± 0.9	7.1 ± 0.9	7.3 ± 1.0	<0.05
	Cholesterol (mmol/L)	4.3 (3.6-5.2)	4.7 (3.8-5.6)	4.1 (3.4-5.0)	<0.05
	PTH (pg/ml)	13.5 (6.0-22.2)	13.4 (6.8-21.4)	13.6 (5.6-22.3)	0.96

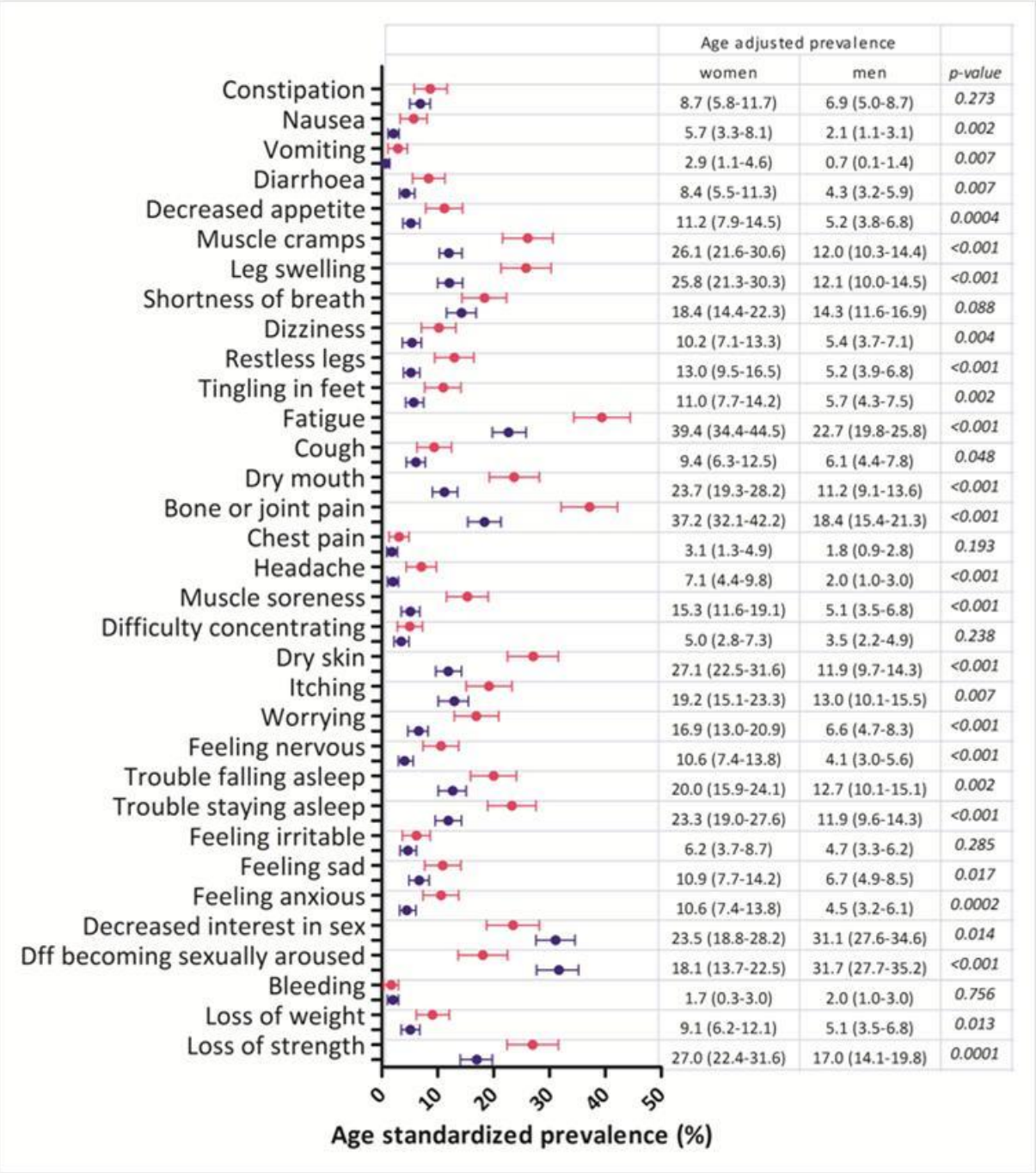
[1] *Data from n=1077 available patient questionnaires*

Figure 1: **Prevalence of uraemic symptoms**



** indicates a significant difference in symptom prevalence between men and women*

Figure 2: **Age adjusted prevalence of the individual uraemic symptoms among women and men**



	Age adjusted prevalence		
	women	men	*p-value*
Constipation	8.7 (5.8-11.7)	6.9 (5.0-8.7)	*0.273*
Nausea	5.7 (3.3-8.1)	2.1 (1.1-3.1)	*0.002*
Vomiting	2.9 (1.1-4.6)	0.7 (0.1-1.4)	*0.007*
Diarrhoea	8.4 (5.5-11.3)	4.3 (3.2-5.9)	*0.007*
Decreased appetite	11.2 (7.9-14.5)	5.2 (3.8-6.8)	*0.0004*
Muscle cramps	26.1 (21.6-30.6)	12.0 (10.3-14.4)	*<0.001*
Leg swelling	25.8 (21.3-30.3)	12.1 (10.0-14.5)	*<0.001*
Shortness of breath	18.4 (14.4-22.3)	14.3 (11.6-16.9)	*0.088*
Dizziness	10.2 (7.1-13.3)	5.4 (3.7-7.1)	*0.004*
Restless legs	13.0 (9.5-16.5)	5.2 (3.9-6.8)	*<0.001*
Tingling in feet	11.0 (7.7-14.2)	5.7 (4.3-7.5)	*0.002*
Fatigue	39.4 (34.4-44.5)	22.7 (19.8-25.8)	*<0.001*
Cough	9.4 (6.3-12.5)	6.1 (4.4-7.8)	*0.048*
Dry mouth	23.7 (19.3-28.2)	11.2 (9.1-13.6)	*<0.001*
Bone or joint pain	37.2 (32.1-42.2)	18.4 (15.4-21.3)	*<0.001*
Chest pain	3.1 (1.3-4.9)	1.8 (0.9-2.8)	*0.193*
Headache	7.1 (4.4-9.8)	2.0 (1.0-3.0)	*<0.001*
Muscle soreness	15.3 (11.6-19.1)	5.1 (3.5-6.8)	*<0.001*
Difficulty concentrating	5.0 (2.8-7.3)	3.5 (2.2-4.9)	*0.238*
Dry skin	27.1 (22.5-31.6)	11.9 (9.7-14.3)	*<0.001*
Itching	19.2 (15.1-23.3)	13.0 (10.1-15.5)	*0.007*
Worrying	16.9 (13.0-20.9)	6.6 (4.7-8.3)	*<0.001*
Feeling nervous	10.6 (7.4-13.8)	4.1 (3.0-5.6)	*<0.001*
Trouble falling asleep	20.0 (15.9-24.1)	12.7 (10.1-15.1)	*0.002*
Trouble staying asleep	23.3 (19.0-27.6)	11.9 (9.6-14.3)	*<0.001*
Feeling irritable	6.2 (3.7-8.7)	4.7 (3.3-6.2)	*0.285*
Feeling sad	10.9 (7.7-14.2)	6.7 (4.9-8.5)	*0.017*
Feeling anxious	10.6 (7.4-13.8)	4.5 (3.2-6.1)	*0.0002*
Decreased interest in sex	23.5 (18.8-28.2)	31.1 (27.6-34.6)	*0.014*
Dff becoming sexually aroused	18.1 (13.7-22.5)	31.7 (27.7-35.2)	*<0.001*
Bleeding	1.7 (0.3-3.0)	2.0 (1.0-3.0)	*0.756*
Loss of weight	9.1 (6.2-12.1)	5.1 (3.5-6.8)	*0.013*
Loss of strength	27.0 (22.4-31.6)	17.0 (14.1-19.8)	*0.0001*

Figure 3: **Age adjusted prevalence for factors related to the clinical condition of women and men**